due to slow patient accrual are, in part, responsible for the slow progress in this area. Participation of international centers in multicenter clinical trials is needed. Towards this effort, a Brazil-Seattle chronic GVHD consortium was established to conduct collaborative studies, which included a survey of chronic GVHD after allogeneic hematopoietic cell transplantation (allo-HCT) performed in Brazil.

Method: Thirty-six transplant services registered with the Brazilian Society of Bone Marrow Transplantation were invited to participate in a web-based survey containing 36 questions about routines and major outcomes of allo-HCTs performed in 2008.

Results: Seventeen (47%) centers performed allo-HCTs in 2008 and completed the survey between May and September 2010. The 17 responding centers have been performing allogeneic transplants for a median of 16 (range, 7-31) years. Among the 17 centers, the median number of allogeneic transplants reported in 2008 was 21 (range, 5-116), of which 91% were from a related donor. The median number of adult allo-HCTs was 16 (range, 2-84) and the median numbers of pediatric allo-HCTs was 3 (range, 0-51). Of the reported 510 allo-HCTs in 2008, near 60% were performed at four centers. For classification of chronic GVHD, 50% reported using the NIH criteria, 37% the Seattle revised classification and 12% both criteria. Eighty-eight percent of the centers reported performing chronic GVHD screening evaluation between days 80 -100 after HCT. Three centers reported seeing > 12 new cases of chronic GVHD in one year, 5 reported seeing 6-12 patients, and 9 centers reported seeing < 6 new cases. The overall disease-free survival (DFS) rates at 100 days were > 75% (7 centers), 50-75% (9 centers) and 26-50% (1 center). The overall DFS at 1-year was 50-75% as reported by 13 centers and was 26-50% as reported by 4 centers. The table summarizes the types of primary and secondary treatments reported for chronic GVHD.

Conclusion: The variability in diagnosis and treatment of chronic GVHD in Brazilian Centers is similar to that previously reported by American and European centers. The Brazil-Seattle chronic GVHD consortium network exemplifies the feasibility of collaborative research across the international borders of Western hemisphere and offers new opportunities for future collaborative studies.

Table 1. Chronic GVHD therapy reported

Therapy	First Line (%*)	Second Line (%*)
Steroid 1mg/kg/day	100	19
Cyclosporine	75	44
Tacrolimus	25	31
Mycophenolate mofetil	-	94
PUVA	-	62
ECP (photopheresis)	-	44
Thalidomide	-	44
Azathioprine	-	25
Sirolimus	-	12
Anti-CD20 antibody	-	12

*Frequency of therapy prescribed.

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GENITAL GRAFT VERSUS HOST DISEASE: ACUTE VERSUS EARLY ONSET CHRONIC DISEASE

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Background: While genital chronic graft versus host disease (cGVHD) has become better characterized, genital acute GVHD (aGVHD), a rarer entity, remains poorly understood.

Objective: To describe genital aGVHD in a cohort with genital GVHD.

Methods: A cohort of 68 women were diagnosed with genital GVHD. Among these 68, some with gynecologic symptoms were assessed within 100 days post-transplant as part of transplantation protocols. We evaluated time from hematopoietic cell transplant (HCT), other GVHD manifestations, gynecologic history, vulvar/vaginal findings, clinical course and treatment to better characterize genital aGVHD.

Results: Of 68 patients, 6 were diagnosed with genital GVHD prior to 100 days post-HCT (median 79: range 14-92). Of these 6 patients, 4 were diagnosed with aGVHD involving the skin (2) or skin and gastrointestinal tract (2) prior to diagnosis of genital aGVHD (median 29.5: range 6-54 days). One other patient presented with genital aGVHD the day before skin aGVHD was diagnosed. Only 1 genital aGVHD patient had no other tissue site of involvement. Only 1 patient had an early donor lymphocyte infusion, which was administered at 42 days post-HCT; this patient was diagnosed with genital aGVHD at 92 days post-HCT. 5 of 6 patients (83.3%) had Grade II genital GVHD at presentation (as defined by Stratton et al 2009), while one patient presented with Grade I disease. These Grade II patients were treated with topical clobetasol or topical tacrolimus. Of these 5 treated patients, 4 returned for follow-up care. Over a one-year observation interval, one patient had a complete response, one patient had a partial response, and two patients progressed from Grade II to Grade III disease. One patient with vaginal synechiae was treated with an estradiol vaginal ring, with complete response observed.

Conclusions: Our findings indicate that genital GVHD can occur before 100 days after allogeneic HCT. Considering that 5 of 6 (83%) affected patients in this series had acute GVHD of other organ systems, gynecologic issues should be included in the GVHD evaluation of female transplant patients. Finally, because genital aGVHD was, in general, amenable to topical treatments, our findings offer hope that with appropriate diagnosis and intervention, genital aGVHD can be effectively treated to improve the quality of life of female transplant survivors.

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A PILOT STUDY OF PHARMACOKINETICS-BASED MYCOPHENOLATE MOFETIL DOSING FOR ACUTE GRAFT-VERSUS-HOST-DISEASE PROPHYLAXIS

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Mycophenolate mofetil (MMF) is an ester prodrug of mycophenolic acid (MPA) which has been used successfully in the prevention and treatment of acute graft-versus-host-disease (aGVHD). Previous pharmacokinetics (PK) studies have shown low MPA exposure in BMT recipients, especially in the period following conditioning therapy, which is associated with inferior transplant outcomes. Multiple strategies, including empiric fixed-dose-escalation or higher dose per kg body weight, have failed to achieve consistent target MPA exposure. Attempts at giving MMF as short-infusion doses have been unsuccessful in maintaining desired trough concentrations (Ctrough) of MPA, especially in pediatric BMT patients. We hypothesized that a PK-based dosing strategy using a novel continuous infusion of MMF will be able to achieve and maintain target MPA exposure. The primary aim of this pilot study is to evaluate the safety and feasibility of this approach.

Continuous infusion MMF was evaluated in 5 pediatric patients undergoing unrelated donor myeloablative transplant between July, 2009 and June, 2010. Mean age was 8.5 y (2-17 y) (4 F, 1 M). Patient diagnoses were MDS (2), ALL in CR2, Kostmann syndrome, and congenital erythropoietic porphyria. Three patients received MMF for GVHD prophylaxis and two for treatment of severe aGVHD. In all cases, total MPA Ctrough levels remained < 1 mcg/mL with intermittent IV dosing (15 mg/kg/dose q8 hourly). PK measurements on this schedule were used to estimate MPA clearance in order to predict the rate of a continuous infusion to maintain total MPA steady-state concentrations (Css) between 2.5-5 mcg/mL. Rates of infusion used ranged

from 38-96 mg/kg/day. Total MPA Css concentrations ranged between 1.1-3.9 mcg/mL (mean 2.17 ± 0.76 mcg/mL). Total MPA steady-state clearance (CLss) values ranged between 7.8-28.6 mL/min/kg. Therapeutic total MPA Css levels were maintained in these patients for a duration of 10-30 days. Patients tolerated the infusion well and no infusion-related reactions or other adverse events occurred.

In conclusion, we show that continuous infusion of MMF is safe and feasible, and successfully achieves and maintains targeted steady-state concentrations of MPA. We have extended our pilot protocol in order to study the clinical impact and pharmacokinetics of a continuous infusion of MMF for GVHD prophylaxis on a larger and more diverse pediatric BMT population in our institution.

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DYNAMICS OF DONOR T CELL ACTIVATION DURING EARLY PHASE OF GRAFT VERSUS HOST DISEASE (GVHD): DONOR ANTIGEN PRESENTING CELLS CAN ACTIVATE ALLOGENEIC T CELLS

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Graft-versus-host disease (GVHD) is a major complication to hematopoietic stem cell transplantation (HSCT). The role of host antigen presenting cells in the activation of donor T-cells has been reported previously. In the present investigation we tracked host and donor immune cells in a chronological approach to determine phenotypical and biological activation patterns during early stages of GVHD.

Female BALB/c mice were conditioned using busulfan and cyclophosphamide and transplanted using either male C57BL/6 (allogeneic) or BALB/c (syngeneic) donors. Recipient mice were killed at day 0,+1,+3,+5,+7 and +21 post BMT; spleen and BM were assessed for phenotype and function of immune cells. Serum cytokines were measured and histopathology and immunohistochemistry examinations were carried out to confirm emergence of GVHD.

GVHD occurred 7 days after allogeneic BMT. Donor dendritic cells (DCs) significantly expanded and matured early after allo-BMT (day+3) compared to that observed for host DCs expansion. T-cells repopulation was similar in both allogeneic and syngeneic group until day+3. However, donor CD8+ cell expansion, five days after BMT was 230% compared to that observed in control. IL2, IFN-gamma and TNF-alfa were at the highest level at day +5 which were compatible with T-cell activation. Upon activation most of naïve T-cells gain effector-memory phenotype and migrated from the spleen to periphery.

Tracking of host versus donor immune cell at early phase of GVHD have shown that donor DCs has essential role in the activation of donor allogeneic T-lymphocyte. Moreover, during activation phase of T-cells in the spleen donor naïve cells gain effector-memory phenotype and initiate GVHD.

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IS IT IMPORTANT TO PERFORM LIVER BIOPSY AFTER ALLOGENEIC TRANSPLANTATION?

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Purpose: to evaluate how often was liver impairment caused due to graft versus host disease after allogeneic transplantation.

Methods: From year 2004 to 2007 we performed liver biopsy in 17 patients (pts) because of the liver impairment after allogeneic stem cell transplantation. The biopsy was performed in each patient every time, we could not state the diagnosis from blood tests for sure.

We confirmed GVHD etiology just in 11pts (65%). 4 pts was diagnosed with toxic liver impairment, probably due to wide range of medication. 1 patient was diagnosed with sinusoidal obstructive syndrome and in 1 case we proved EBV affection in combination with autoimune hepatitis. There was no liver failure or progression of liver function test in 6 pts, which we did not treat as GVHD according to the biosy finding. As for liver function testing (bil, ALT, AST, ALP, GMT) we did not find any important diference in this two cohort of pts. Pts with GVHD and other had nearly simmilar laboratory results in the time of biopsy.

It was interesting, that in histology examination we proved severe liver hemosiderosis in 8pts (47%) and moderate liver hemosiderosis in 5pts (29%). In 6 pts we were also able to evaluate iron storage in liver tissue, it was increased in each case, in some cases there was very severe iron overload (range 2860- 11310 mikrog/g with median 5134 mikrog/g). It corelated with serum ferritin level, wchich was in range from 1930- 23123 mmol/kg with median 6256mmol/kg.

There was no complication after liver biopsy. In most cases we performed classical transparietal biopsy. When transjugular biopsy was performed, there was often no bile duct in the specimen of liver, and as this is really important for right diagnosis, we had to do re-biopsy in some cases.

Conclusion: we conclude, that after allogeneic transplantation is really important to do the liver biopsy and not to treat pts with immunosupression without histological confirmation. It is also very important to evaluate the liver storage of iron, because most patient is heavy overload.

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THE ECONOMIC BURDEN OF CHRONIC GRAFT-VERSUS-HOST DISEASE: A RESOURCE UTILIZATION STUDY AMONG ADULT RECIPIENTS OF MATCHED SIBLING DONOR AND UMBILICAL CORD BLOOD HEMATOPOIETIC CELL TRANSPLANTATION

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Chronic graft-versus-host disease (CGVHD) can impair quality of life and is associated with significant morbidity and mortality among allogeneic hematopoietic cell transplant (HCT) recipients.

Table 1. Resource utilizatiom associated with CGVHD in first 2 years post-HCT

Characteristic	MRD	UCB	Controls
N	29	22	45
Median outpatient visits (range)	49 (13-236) days	37 (10-121) days	20 (4-90) days
CMV infection	11 (38%)	8 (36%)	6 (13%)
Fungal infection	5 (17%)	3 (14%)	0
Median IVIG infusions (range)	6 (3-16)	5 (3-14)	1 (1-10)
Median RBC transfusion (range)	14 (2-31)	5 (1-30)	1 (1-3)
Median platelet transfusion (range)	14 (4-168)	7 (1-95)	1 (1-19)
Total hospitalizations*	59	56	16
Median hospitalizations/patient (range)	3 (1-8)	3 (1-12)	1 (1-9)
Median hospital stay/admit (range)	18 (1-139)	25 (4-176)	4 (1-69)

*Hospitalizations occured in 18 (62%) MRD, 15 (68%) UCB and 8 (18%) controls.